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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/643,083	08/19/2003	Andreas Pluckthun	37629-0077	3061

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EXAMINER	
SHIBUYA, MARK LANCE	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 07/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/643,083	PLUECKTHUN ET AL.	
	Examiner	Art Unit	
	Mark L. Shibuya	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *12 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-22* is/are pending in the application.

4a) Of the above claim(s) *20 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-19 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/564,351.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/14/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 16-22 are pending. Claims 20 and 21 are withdrawn from consideration. Claims 16-19 and 22 are examined.

Election/Restrictions

2. Applicant's election of the species of Skp protein or a homologue thereof, periplasmic protein that is a fragment of an immunoglobulin and immunoglobulin fragment that is an scFv immunoglobulin fragment, in the reply filed on 1/30/2006, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 20 and 21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 1/30/2006.

Priority

4. The instant application, filed 8/19/2003, states that it is a Divisional of 09/564,351, filed 5/1/2000, now US Patent 6,630,317, issued 10/7/2003 (amendment to the specification, entered 11/19/2003). The instant application claims foreign priority of

EP application 97118457.7, filed 10/23/1997 and claims foreign priority of WIPO application PCT/EP98/06755, filed 10/23/1998, (application data sheet entered 8/19/2003).

5. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 and 121 as follows:

The examiner respectfully submits that the specification as filed does not provide support for the claim limitation, added by amendment, to a nucleic acid sequence encoding a "periplasmic protein heterologous to a bacterial cell", as in new claim 16. Therefore, the effective filing date of the instant claimed invention is considered to be 8/19/2003.

Furthermore, the examiner respectfully submits that the instant application is not a divisional of application 09/564,351, filed 5/1/2000, because the claims of the instant application are not of an Invention of a group that was restricted in the '351 application. The '351 records a requirement for election/restriction, mailed 6/4/01, that restricts between Group I, claims 1-8, drawn to a method of obtaining a nucleic acid sequence comprising a polypeptide coding sequence and screening for the expression thereof, and Group II, claims 9-15, drawn to a method increasing the expression of a periplasmic protein by co-expression the periplasmic protein and an identified polypeptide. In the Reply, entered 6/29/2001, applicant elected Group II in the '351 application. However,

neither of said Group I or Group II are drawn to the Invention of instant claims 16-22, drawn to a co-expression system comprising a first nucleic acid sequence encoding a periplasmic protein heterologous to a bacterial cell, and a second nucleic acid sequence encoding a bacterial polypeptide that enhances the folding of said periplasmic protein. Because the invention of the instant claims was not subject to restriction in the parent '351 application, the instant application is not a divisional of the parent application.

6. Receipt is acknowledged of certified papers of the EP application 97118457.7, filed 10/23/1997, submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file of the parent application 09/564,351, filed 5/1/2000. Acknowledgment is made of applicant's claim for foreign priority based on WIPO application PCT/EP98/06755, filed 10/23/1998. It is noted, however, that applicant has not filed a certified copy of the PCT/EP98/06755 application as required by 35 U.S.C. 119(b).

Information Disclosure Statement

7. The information disclosure statement filed 1/14/2004 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because citation no. A08, Buchner, does not provide the name of the journal, volume, and page numbers. It has been placed in the application file, but the information referred to therein to citation A08 has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement

or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

8. Cite no. A28 appear to be a duplicate of cite no. A03, and is crossed off.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 16-19 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is for new matter.

The specification as filed does not appear to provide support for the newly added claim limitation of a nucleic acid sequence encoding a "periplasmic protein heterologous to a bacterial cell", as in new claim 16. Applicant must point, with particularity, where specific support may be found in the specification as filed, for this limitation to the claimed invention.

11. Claims 16-19 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is for lack of written description.

The claims are drawn to a co-expression system comprising a first nucleic acid sequence and a second nucleic acid sequence, wherein said first nucleic acid sequence encodes a periplasmic protein heterologous to a bacterial cell, and wherein said second nucleic acid sequence encodes a bacterial polypeptide that enhances the folding of said periplasmic protein in said bacterial cell; and variations thereof.

The MPEP states:

> The first paragraph of 35 U.S.C. 112 requires that the "specification shall contain a written description of the invention * * *." This requirement is separate and distinct from the enablement requirement. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1114 (Fed. Cir. 1991). >See also *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 920-23, 69 USPQ2d 1886, 1890-93 (Fed. Cir. 2004) (discussing history and purpose of the written description requirement); *In re Curtis*, 354 F.3d 1347, 1357, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004) ("conclusive evidence of a claim's enablement is not equally conclusive of that claim's satisfactory written description").< The written description requirement has several policy objectives. "[T]he essential goal' of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." *In re Barker*, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). Another objective is to put the public in possession of what the applicant claims as the invention. See *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089 (1998). The written description requirement of the Patent Act promotes the progress of the useful art by ensuring that patentees adequately describe their inventions in their patent specifications in exchange for the right to exclude others from practicing the invention for the duration of the patent's term.

MPEP 2163. The MPEP further states:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, . . . reduction to drawings, . . . or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus . . . . See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> . . .
>
> . . . A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. >The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated.").

MPEP 2163.

The description of the instant specification does not clearly convey to the practitioner that the applicant had possession of the subject matter that is claimed. The claims and the specification do not describe what structural or sequential features are possessed by a first nucleic acid that encodes a periplasmic protein heterologous to a bacterial cell. A periplasmic protein would appear to any protein that is capable of being produced into the periplasmic space of certain bacteria, however, the specification as filed does not describe what structures or sequences are responsible for this property.

Furthermore, the limitation that the periplasmic protein must be heterologous to a bacterial cell, would depend on which bacteria produced the periplasmic protein, so that there is no a priori sequence or structure that would serve to describe such a heterologous protein. Furthermore, the specification does not provide description for any fragment of an immunoglobulin or any fragment of an scFv immunoglobulin fragment. It is respectfully noted that such a fragment could be one amino acid, or a peptide dimer, or some portion thereof.

Because the claims appear do not appear to meaningfully limit the proteins encoded by the first nucleic acid, the examiner respectfully submits that the specification does not describe a representative number of species of nucleic acids encoding proteins so that one of skill in the art would envision that the applicant had possession of the genus of first nucleic acids encoding a periplasmic protein heterologous to a bacterial cell.

The claims are also drawn to a second nucleic acid that encodes a bacterial polypeptide that enhances the folding of the periplasmic protein in the bacterial cell. Dependent claim 18, for example, are drawn to nucleic acids encoding a nucleic acid encoding an immunoglobulin fragment. At the time the specification was filed, the art taught many different polypeptides, including bacterial polypeptides that supported the folding of proteins, (see, e.g., Gething et al., Nature, vol. 355, 2 Jan. 1992, pp. 33-45, especially at Tables 1 and 2). However, it is unpredictable as to which folding peptides will fold a particular peptide. See, e.g., Berges et al., Applied and Environmental

Microbiology, Jan. 1996, vol. 62, no. 1, pp. 55-60; Wall et al., Current Opinion in Biotechnology, 1995, vol. 6, pp. 507-516, (IDS entered 1/14/2004, cite no. A42).

In considering that "there is no general effect of any of the three chaperone plasmids when tested with the four cytokine constructs", Berges et al., at p. 60, states that because "it is still not possible to predict which combinations will be successful, any further improvement will require methodical testing of a larger number of different associations."

Wall et al., at p. 514, states that for each success story in folding several heterologous proteins in *E. coli*, "there are many more (often unpublished) failures at present, and it is this unpredictability which dictates that, for now, the generation of a better understanding of *E. coli*'s protein folding mechanisms remains a priority. the hope is obviously that a clearer picture of the *in vivo* process will point the way to a more rational approach to improving the folding of heterologous protein in *E. coli*."

Therefore, the examiner respectfully submits that the specification does not describe a representative number of species of second nucleic acids encoding proteins so that one of skill in the art would envision that the applicant had possession of the genus of nucleic acids encoding a bacterial polypeptide that enhances the folding of the periplasmic protein in the bacterial cell.

12. Claims 16-19 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a first nucleic acid

sequence encoding an immunoglobulin scFv, and a second nucleic acid sequence encoding Skp protein or FkpA protein, does not reasonably provide enablement for compositions comprising a first nucleic acid sequence and a second nucleic acid sequence, wherein said first nucleic acid sequence encodes a periplasmic protein heterologous to a bacterial cell, and wherein said second nucleic acid sequence encodes a bacterial polypeptide that enhances the folding of said periplasmic protein in said bacterial cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to a co-expression system comprising a first nucleic acid sequence and a second nucleic acid sequence, wherein said first nucleic acid sequence encodes a periplasmic protein heterologous to a bacterial cell, and wherein said second nucleic acid sequence encodes a bacterial polypeptide that enhances the folding of said periplasmic protein in said bacterial cell; however, there is insufficient guidance as to how to make and use any protein heterologous to a bacterial cell or a bacterial polypeptide that enhances the folding of said periplasmic protein in said bacterial cell. There are many factors be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether undue experiment is necessitated. These factors can include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the relative skill of those in the art;

(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1 and 2) The breadth of the claims and the nature of the invention:

The claims are drawn broadly to a co-expression system comprising a first nucleic acid sequence and a second nucleic acid sequence, wherein said first nucleic acid sequence encodes a periplasmic protein heterologous to a bacterial cell, and wherein said second nucleic acid sequence encodes a bacterial polypeptide that enhances the folding of said periplasmic protein in said bacterial cell; and variations thereof.

(3 and 5) The state of the prior art and the level of predictability in the art:

it is unpredictable as to which folding peptides will fold a particular peptide. See, e.g., Berges et al., Applied and Environmental Microbiology, Jan. 1996, vol. 62, no. 1, pp. 55-60; Wall et al., Current Opinion in Biotechnology, 1995, vol. 6, pp. 507-516, (IDS entered 1/14/2004, cite no. A42).

In considering that "there is no general effect of any of the three chaperone plasmids when tested with the four cytokine constructs", Berges et al., at p. 60, states that because "it is still not possible to predict which combinations will be successful, any further improvement will require methodical testing of a larger number of different associations."

Wall et al., at p. 514, states that for each success story in folding several heterologous proteins in *E. coli*, "there are many more (often unpublished) failures at present, and it is this unpredictability which dictates that, for now, the generation of a better understanding of *E. coli*'s protein folding mechanisms remains a priority. the hope is obviously that a clearer picture of the *in vivo* process will point the way to a more rational approach to improving the folding of heterologous protein in *E. coli*.

(4) The level of one or ordinary skill: The level of skill would be high, most likely at the Ph.D. level. However, such persons of ordinary skill in this art, *given its unpredictability*, would have to engage in undue (non-routine) experimentation to carry out the invention as claimed.

(6-7) The amount of direction provided by the inventor and the existence of working examples:

The specification, at pp. 16-25, Experiments 1 and 2, disclose working examples of co-expression of a first nucleic acid sequence encoding Skp protein or FkpA protein, and scFv immunoglobulin fragment, in a phage display system.

The claims and the specification do not provide guidance or direction as to what structural or sequential features are possessed by a first nucleic acid that encodes a periplasmic protein heterologous to a bacterial cell. A periplasmic protein would appear to any protein that is capable of being produced into the periplasmic space of certain bacteria, however, the specification as filed does not provide guidance or direction for what structures or sequences are responsible for this property. Furthermore, the specification does not provide guidance or direction for any fragment of an

immunoglobulin or any fragment of an scFv immunoglobulin fragment. It is respectfully noted that such a fragment could be one amino acid, or a peptide dimer, or some portion thereof.

Furthermore, the limitation that the periplasmic protein must be heterologous to a bacterial cell, would depend on the species of bacteria in which the periplasmic protein was produced, and the specification does not provide guidance or direction as to which nucleic acids would encode such a heterologous protein. Because the claims appear do not appear to meaningfully limit the polypeptides encoded by the first nucleic acid, the examiner respectfully submits that the specification does not teach how to make and use the full scope of the claimed invention.

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure:

The instant specification does not provide to one skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed in carrying out the full scope of the claimed methods. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vick*, 947 F.2d 488, 496 and n.23, 20 USPQ2d 1438, 1455 and n.23 (Fed. Cir. 1991). Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure, undue experimentation would be required of one of skill in the art to practice the full scope of the claimed invention.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 16-19 and 22 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The preamble of Claim 16 recites the term "system", which renders the claims vague and indefinite, because the term is capable of different meanings, including a product that comprises a first and second nucleic acid sequence, or a method of enhancing the folding of a periplasmic protein.

Claim Rejections - 35 USC § 101

15. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

16. Claims 16-19 and 22 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to a "system", which is not a class of statutory subject matter.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

18. Claims 16-19 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Pluckthun et al., WO 99/22010.

The claims are drawn to a co-expression system comprising a first nucleic acid sequence and a second nucleic acid sequence, wherein said first nucleic acid sequence encodes a periplasmic protein heterologous to a bacterial cell, and wherein said second nucleic acid sequence encodes a bacterial polypeptide that enhances the folding of said periplasmic protein in said bacterial cell.

Pluckthun et al., WO 99/22010, throughout the publication and abstract, teach vectors comprising a first nucleic acid sequence and a second nucleic acid sequence, wherein said first nucleic acid sequence encodes a scFv-fragment (see e.g., p. 13, para 4) which, absent evidence to the contrary, reads on a periplasmic protein heterologous to a bacterial cell, and wherein said second nucleic acid sequence encodes Skp, (see,

e.g., p. 13, para 3) which, absent evidence to the contrary, reads on a bacterial polypeptide that enhances the folding of said periplasmic protein in said bacterial cell.

19. Claim 16 is rejected under 35 U.S.C. 102(b) as being anticipated by Perez-Perez et al., Biochemical and Biophysical Research Communications, 16 May 1995, Vol. 210, No. 2, pp. 524-529.

Perez-Perez et al., throughout the publication, and at the abstract, and p. 525, teach E. coli containing a nucleic acid OmpA plasmid encoding hG-CSF cDNA (human granulocyte-colony stimulating factor, (which, absent evidence to the contrary, reads on a periplasmic protein heterologous to a bacterial cell) and plasmids encoding groES/groEL or DnaK/DnaJ, which, absent evidence to the contrary, read on bacterial polypeptides that enhances the folding of said periplasmic protein in said bacterial cell.

20. Claim 16 is rejected under 35 U.S.C. 102(b) as being anticipated by Duenas et al., Bio/Technology, 1994, Vol. 16, No. 3, pp. 476-483.

Duenas et al., throughout the publication, and abstract, teach bacterial strains transformed with a vector carrying the genes encoding variable regions of an anti-CEA scFv antibody and the ompA leader sequence, reading on vectors comprising a first nucleic acid sequence and a second nucleic acid sequence, wherein said first nucleic acid sequence encodes a periplasmic protein heterologous to the bacterial cell (i.e., the

scFv antibody), and wherein said second nucleic acid sequence encodes a bacterial polypeptide (i.e., the ompA leader sequence) that enhances the folding of said periplasmic protein in said bacterial cell.

21. Claims 16-19 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Missiakas et al., Molecular Microbiology (1996), Vol. 21, No. 4, pp. 871-884, (IDS entered 1/14/2004, cite no. A03).

Missiakas et al., (1996), (IDS entered 1/14/2004, cite no. A03), throughout the publication, and abstract, and at p. 881, teach a p15A-based vector pOK12 comprising a ompH (skp) gene, (see, also, p. 872, para 3; p. 876, para 3-p. 877, para 2), reading on vectors comprising a first nucleic acid sequence and a second nucleic acid sequence, wherein said first nucleic acid sequence encodes at least one amino acid that, absent evidence to the contrary, reads on a fragment of an immunoglobulin (as in claims 17, 18, and 22), and therefore a periplasmic protein heterologous to the bacterial cell of claim 16, and wherein said second nucleic acid sequence encodes a the Skp protein, as in claims 19 and 22, that reads on a bacterial polypeptide that enhances the folding of said periplasmic protein in said bacterial cell.

Double Patenting

22. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

23. Claims 16-19 and 22 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 6, 7, 11, and 12 of U.S. Patent No. 6,630317. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Instant claims are drawn to a co-expression system comprising a first nucleic acid sequence and a second nucleic acid sequence, wherein said first nucleic acid sequence encodes a periplasmic protein heterologous to a bacterial cell, and wherein said second nucleic acid sequence encodes a bacterial polypeptide that enhances the folding of said periplasmic protein in said bacterial cell; and variations thereof. Thus the claims of the instant application are not patently distinct from methods for increasing the expression of a heterologous periplasmic protein in functional form in a bacterial host cell comprising providing host cells comprising a first nucleic acid sequence encoding

and expressing polypeptides and a second nucleic acid encoding heterologous periplasmic protein, as in independent claims 1 and 11 of the '317 patent.

Instant dependent claims 17 and 19, drawn to a co-expression system wherein the bacterial polypeptide is the Skp protein, the FkpA protein, and homologues thereof, and the heterologous periplasmic polypeptides is a scFv immunoglobulin fragment; is not patently distinct from the method of the '317 patent comprising *E. coli* protein Skp, FkpA, and homologues thereof, (as in claims 3 and 4 of the '317 patent). Instant dependent claims 18 and 22, drawn to a co-expression system wherein the heterologous, periplasmic protein is an immunoglobulin or a fragment thereof, and wherein the immunoglobulin fragment is a scFv immunoglobulin fragment; is not patently distinct from the method of the '317 patent comprising protein comprising a domain of the immunoglobulin superfamily, and wherein the immunoglobulin fragment is scFv, (as in claims 6, 7, and 12 of the '317 patent).

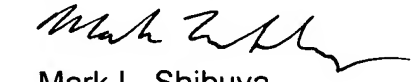
Conclusion

24. Claims 16-19 and 22 are rejected.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Mark L. Shibuya
Examiner
Art Unit 1639